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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/460,920	PIPER, BETH ANNE	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,45,48,53,54,72,75-78 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,45,48,53,54,72,75-78 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of amendments/remarks on 07/03/08. By the amendment, claims 37 and 72 have been amended and claims 46 and 47 have been cancelled; Claims 37, 45, 48, 53-54, 72, 75-78 and 80 are currently pending for prosecution on the merits.

2. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 37, 45, 48, 72, 75-78 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims in this application recite limitation, namely "metformin…up to about 750mg" or "metformin…at most about 750mg" and "glyburide… up to about 15mg". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

The scope of the instantly claimed range of metformin and glyburide encompasses any dosage amounts up to 750mg of metformin and up to 15mg of glyburide. For instance, 100mg of metformin and 0.1 mg of glyburide fall within the claimed dosage range of metformin and glyburide respectively.

The specification discloses that "the low dose pharmaceutical formulation will be preferably be employed in first line therapy in a daily dosage to provide less than about 500 mg metformin per day, preferably no more than about 750mg metformin per day, preferably no more than about 500 mg metformin per day, and a starting dosage of from about 160 to about 500mg per day, preferably 250mg per day or 500 mg per day, in single or divided doses of one to four tablets daily" (page 8, lines 15-23); and that "the glyburide is employed in starting daily dosage as low as about one-fifth of the starting daily dosage of glyburide employed in generally accepted medical practice….(that is a minimum starting daily dosage as low as 0.5mg)" (page 8, lines 24-29).

Therefore, it would have been clear to one skilled in the art, reading the instant disclosure, that the lowest daily dosages of metformin and glyburide required for this invention about 160mg and 0.5mg respectively.

As stated above, the ranges of daily dosage amount of metformin and glyburide introduced by the amendment, for example less than 160mg of metformin and less than 0.5mg of glyburide cannot be found in the specification and introduce new concepts and violate the description requirement of the first paragraph of 35 USC 112.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 37, 45, 48, 53-54, 72, 75-78 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barelli et al.(WO 97/17975, pub date: May 22, 1997, equivalent to US Patent 5,922,769) in view of Bauer et al. (US Patent 5,258,185, issue date: Nov. 2, 1993), and further in view of Drug Facts and Comparisons (1995 Edition, pp. 547) and Shell et al. (US 6340475).

The amended claims are directed to a method of treating type 2 diabetes comprising administering to a drug naive human patient, as first line therapy, a low dose of a combination of metformin and glyburide where the daily dosage of metformin is 250mg; the daily dosage of glyburide is 1.25mg, wherein after the starting (initial) daily dosage, the metformin in said combination is administered in an amount up to about 750mg and the glyburide in said combination is administered in amount up to about 15mg, and wherein the weight ratio of

metformin to glyburide is about 200:1. Further limitations include metformin and glyburide is formulated as a single dosage form (claim 45); "one to four times daily" or "once a day or twice a day" (claim 48 and 53 respectively); "a baseline haemoglobin A1c (HbA1c) >9% or a fasting glucose > 200mg/dlL twice daily…" (claim 54); and the glyburide having particular particle size or particle distributions and the patient population being drug naive patients as recited in the claims.

Barelli et al. teach a combination of metformin and glibenclamide (glibenclamide and glyburide are synonymous), in a weight ratio higher than 1:100, being useful for the treatment of type II diabetes (claims) and that the combination makes the therapeutical effect optimum at any time of the progression of the disease, starting from the onset of the disease in NID diabetics (column 3, lines 19-20 and 49-50). Barelli et al. also disclose that the weight ratio of metformin and glibenclamide is about 200:1 (claim 2) which overlaps with the claimed weight ratio; that said combination of dosages can be used starting from the onset of the disease in NID diabetics as long as the ratio of (higher than) 1:100 ratio between the two active principles is maintained, in both the multiple and submultiple dosages (column 3, lines 49-52 and 59-62); that "when the tablets are subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced..." (column 3, lines 52-55); that "the therapeutic rationale of said studies suggested the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition" (column 1, lines 48-55); and that "the combined therapy (sulfonylurea+biguanide) palys therefore a specifically important therapeutical role, since it allows to obtain an effective metabolic control in those patients with diabetes of type II, in which the therapy with only sulfonylureas or only biguanides

becomes ineffective with time" (column 1, lines 62-67). Barelli et al. further teach a single coated tablet in EXAMPLE 1 (column 9, lines 25-26) which contains 500 mg metformin and 5 mg glibenclamide; and that the ratio 5 mg of glibencalimde+500mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclaimde to metformin ratio, even when fractions, will turn out t o be very well balanced (column 7, lines 58-63).

Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of $\pm$5 μm which overlaps with the instantly claimed particle size of 2- 60 μm.

Facts and Comparisons is being supplied as a supplemental reference to demonstrate the state of art knowledge in using 1.25 mg glyburide as a known antidiabetic agent (for patient who may be more sensitive to hypoglycemic drugs).

Shell is being provided as a supplement reference to demonstrate the state of art knowledge in preparing metformin in various dosage forms including 125mg and 250 mg (Example 1).

The difference between Barelli et al.'s teaching and the instant claimed invention lies in that Barelli et al. do not explicitly teach (i) the patient population being drug naive patients or the first line treatment of diabetes, (ii) a low dose of a combination of 250mg and 1.25mg glyburide as starting dosage, (iii) so that daily dosages of glyburide and metformin are up to 15mg and 750mg respectively and (iv) glyburide having particular particle distributions.

With regard to the patient population, although Barelli et al. do not explicitly teach that the combination is administered to a drug naive patient as a first line therapy, Barelli et al. does disclose that the combination teaches a therapeutic effect for treating type 2 diabetes, optimum at any time of the progression of the disease, starting from the onset of the disease in NID diabetics. Since the patient population of Barelli et al.'s method of treatment is type 2 diabetic, without identifying a patient's drug status and treatment history, one having ordinary skill in the art still would have been motivated to treat a drug naïve patient with Barelli et al.'s combination of metformin and glyburide as a first line therapy. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the treatment of Barelli et al. in view of Bauer et al. to result in the practice of the instant invention with a reasonable expectation of success.

With respect to the determination of metformin dosage being 250 mg and glyburide dosage being 1.25 mg, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. discloses "the ratio 5mg of glibenclaimde+500mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclaimde to metformin ratio, even when fractioned, will turn out to be very well balanced" (column 7, lines 58-63). Thus, one having ordinary skill in the art would have been motivated to determine optimum therapeutic combination dosage amounts of metformin and glyburide to treat drug naive patient, e.g., when 5mg of glibenclamide+500mg of metformin is subdivided into half (1/2) or quarter (1/4) amount, 2.5mg of glibenclamide and

250mg of metformin combination or 1.25mg of glibenclamide and 125mg of metformin combination can be prepared and used for the treatment of type II diabetes patient from its onset. Coupled with the above discussed dosage amounts intended for the treatment of the drug naive patient, one having ordinary skill in the art would have understood in light of Barelli (claims 1 and 2) that the weight ratio of meformin and glibenclaimde combination as long as maintained between 100:1 to 200:1 is useful for the treatment of type II diabetes from its onset.

One having ordinary skill in the art would have understood in light Barelli that the subdivided and lower and/or fractional daily dosage of 5 mg of glibencamide+500 mg of metformin, for example 2.5mg of glibenclamide and 250mg of metformin combination or 1.25mg of glibenclamide and 125mg of metformin combination, or any fractions as long as maintained between 100:1 and 200:1, is useful for the less severe cases including diabetes patients from its onset (naive patient).

Furthermore, one having ordinary skill would have expected as taught by Barelli, Drug Facts and Comparisons (1995 Edition, pp. 547) and Shell combination that initiating therapy with low dose of 1.25 mg glyburide and 125mg or 250mg of metformin would be useful for the treatment of type 2 diabetes mellitus patient, especially for patients who are more sensitive to hypolgycemic drugs.

With respect to the recitation of metformin dosage as being up to 750 mg and glyburide dosage as being up to 15 mg, as discussed above, the range of the subdivided and lower and/or fractional daily dosages suggested by Barelli for “the less severe cases” or “the disease from its onset” overlaps with the instantly claimed dosage range. The determination of the appropriate

dosage amounts of active ingredients for a treatment is routinely made by those of ordinary skill in the art and is well within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information of the active ingredient disclosed in the prior art. Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to determine the amounts of metformin and glyburide for achieving the therapeutic effect of treating type 2 diabetes without significant adverse effects to result in the pharmaceutical composition as claimed with a reasonable expectation of success.

Applicant's attention is further drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage range is the optimum combination of percentages.., where the general condition of a claim are disclosed in the prior, it is not inventive to discover the optimum or workable ranges by routine experimentation."

With respect to the specific particle distribution of glyburide, Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of $\pm$5 μm which overlaps with the instantly claimed particle size of 2- 60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that

glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). Although the prior art does not discloses the instant "at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm". However, one having ordinary skill in the art would have expected at the time of the invention was made that the specific particle distribution percentage of the instant claims would have been characteristic of the modified prior art method. Generally, differences in a particle distribution percentage or concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such particle distribution concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable particle distribution percentage or concentration by routine experimentation.

With respect to the recitation of claim 54 regarding patient baseline measurements, those values are the same as those measured for the type 2 diabetic patient as disclosed by Barelli et al. (column 4, lines 23-29).

With respect to the recitation of "lowering blood glucose in a hyperglycemic human patient, decreasing insulin resistance, decreasing hemoglobinAlc, increasing post-prandial insulin levels or decreasing prandial glucose excursion" in claim 72, since the drug combination of metformin and glyburide is the same as what's disclosed in the prior art and are being

administered to the same patient population, the recited effects are expected and thus do not limit the claims.

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Response to Arguments

5. Applicant's arguments filed 07/03/08 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that Barelli does not disclose or suggest using a low dose of combination of metformin, particularly a maximum 750mg daily, and glyburide. Applicant asserts that Barelli actually teaches away from use of the applicant's weight ratio of its low dose combination of metformin:glyburide 200:1. The applicant alleges that Barelli apparently is suggesting dose more than 750mg/day up to 1500mg/day.

This argument is not found persuasive. Barelli teaches that "the ratio 5mg of glibenclaimde+500mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclaimde to

metformin ratio, even when fractioned, will turn out to be very well balanced" (column 7, lines 58-63). Although Barelli discloses 100:1 weight ratio as the specific embodiment, Barelli also teaches that a weight ratio higher than 100:1 of metformin and glibenclamide combination including a weight ratio of 160:1 to 200:1 of metformin and glibenclamide combination is useful for the claimed invention (claims 1-2).

Based on Barelli, 5mg of glibenclamide+500mg of metformin is subdivided into half (1/2) or quarter (1/4) amount, e.g., 2.5mg of glibenclamide and 250mg of metformin combination or 1.25mg of glibenclamide and 125mg of metformin combination, can be prepared and used for the treatment of type II diabetes patient from its onset. In other words, Barelli implicitly teaches or suggests the use of low dose of metformin and glyburide combination, e.g., range from 125mg and 1.25mg glyburide combination to 500 mg metformin and 5mg glyburide combination, for the treatment of "less severe case", e.g., a drug naive patient whereas more than 500mg metformin+5mg glyburide up to 1500mg metformin+15mg glyburide is reserved for the treatment of patient with more severe diabetic condition. Coupled with the above discussed dosage amounts intended for the treatment of the drug naive patient, one having ordinary skill in the art would have understood in light of Barelli (claims 1 and 2) that the weight ratio of meformin and glibencalimde combination maintained as long as between 100:1 to 200:1 is useful for the treatment of type II diabetes from its onset. Thus, one having ordinary skill in the art at the time of the invention was made would have been motivated to make such modification to determine optimum therapeutic combination dosage amounts of metformin and glyburide to treat drug naive patient. Since the patient population of Barelli et al.'s method of treatment is type 2 diabetic, without identifying a patient's drug status and treatment history, one having ordinary

skill in the art still would have been motivated to treat a drug naïve patient with Barelli et al.'s combination of metformin and glyburide in claimed dosage range as a first line therapy.

In response to the applicant's argument that Barelli makes no mention of particle size distribution of glyburide, the examiner likes to point out that secondary reference (Bauer et al.) makes obvious that the specific particle distribution percentage of the instant claims would have been characteristic of the modified prior art method. As discussed above, Bauer teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of $\pm$5 μm which overlaps with the instantly claimed particle size of 2- 60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). Although the prior art does not discloses the instant "at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm". Generally, differences in a particle distribution percentage or concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such particle distribution concentration is critical. Where the general

conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable particle distribution percentage or concentration by routine experimentation.

Applicant's argument in the response takes the position that the resulting combination would not make Applicant's method obvious since none of the references taken alone or in combination discloses or suggests that the instant combination is as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compare to prior art higher dose combinations.

This argument is not found persuasive. Unlike the applicant's argument, there is no indication in the instant claims that the administration of said combination must essentially treat diabetes as efficacious as prior art higher dose combination or reduce side effects as compared to prior art higher dose combinations. In other words, the objective evidence of nonobviousness is not commensurate in scope with the claims which evidence is offered to support. If the criticality of the instant invention is based on "as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compare to prior art higher dose combinations " as the applicant alleged, such feature must be appeared in the claims so that the examiner give a preamble patentable weight. In absence of such critical element(s) in the claim, the examiner maintains the rejection of the record.

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614